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08/779,767	01/07/97	ZAGHOUANI H	ALLIA.143A

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/779,767	Applicant(s) Zaghouani
	Examiner Julie E. Reeves, Ph.D.	Group Art Unit 1806

☒ Responsive to communication(s) filed on *Sep 5, 1997*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-65* is/are pending in the application.

Of the above, claim(s) *5, 12-21, 25, and 30-65* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6-11, 22-24, and 26-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5 and 7*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I and proteolipid protein in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the search for the groups would be coextensive. This is not found persuasive because applicant has provided no evidence to establish why the requirement for restriction is improper. Concerning the election required between myelin basic protein and proteolytic protein, the response argues that "both myelin basic protein and proteolipid protein comprise myelin antigens". As evidenced by Tuohy et al (J Immunology Vol 142 1523-1527 3/89, PTO 1449, paper no 5, reference W), proteolipid protein contains peptide sequences that "show no similarity to the MBP encephalitogenic determinant for SJL mice" (page 1525, first paragraph). Therefore, one skilled in the art would reasonably conclude that myelin basic protein and proteolipid protein contain unique epitopes and therefore are distinct for patentability. The Examiner apologies for the typographical error of proteolytic in place of proteolipid in the restriction requirement. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensiye and is much more important in evaluating the burden of search. Further, it is doubted that applicant would readily accept the rejection of the process of the elected invention over a reference which relates only to the starting

material. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 5, 12-21, 25 and 30-65 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions, the requirement having been traversed in Paper No. 6. Claims 1-4, 6-11, 22-24 and 26-29 will be examined to the extend that they read upon proteolipid protein.

3. This application contains claims 5, 12-21, 25 and 30-65 drawn to inventions non-elected with traverse in Paper No. 6. A complete response to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) MPEP § 821.01.

Specification

4. The disclosure is objected to because of the following informalities: page 4, lines 26-27 recite pending serial numbers. The status of this US application should be updated.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

5. Claims 1-4, 6-11, 22-24, 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-4, 6-11, 22-24, 26-29 are vague and indefinite for reciting "immunosuppressive agent" and "immunosuppressive factor" as the metes and bounds of the claim cannot be determined. An agent or factor can be anything, a peptide, an organic molecule, an inorganic molecule, a DNA fragment, a plastic, a carbohydrate, etc. Applicant's attention is directed to Ex Parte Tanksley (26 USPQ2d 1384) wherein the Board noted that under 35 U.S.C. 112, second paragraph, the claims must be so definite as to allow the comparison with the available art and must also make it possible for the public to determine from the claims what they encompass. How would one know if the patented claimed was being infringed?

b. Claims 1-4, 6-11, 22-24, 26-29 are vague and indefinite for reciting "an immunomodulating agent" because the term "modulation" reads upon both suppression and enhancement. Claim 1 recites at least one immunosuppressive factor in lines 2 and 3, it is not clear how the claims can encompass an immunoenhancing agent when the compound contains immunosuppressive factors.

c. Claims 4 and 24 are indefinite for reciting "analog" as it is not clear what is encompassed by this term. Does the term "analog" mean peptide with amino acid substitutions or

chemical derivatives? Does the term "analog" mean peptide fragments as small as one amino acid or one amino acid side chain residues? Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

d. Claims 6 and 26 are indefinite for reciting "at least part of one domain of a constant region" as it is not clear what is encompassed by this phrase. Does the phrase mean peptide fragments as small as one amino acid or one amino acid side chain residues from a domain of a constant region? Due to the language "comprising at least part of one domain" the claims appear to read upon protein which share in common just one amino acid of the constant region protein. Accordingly, it is impossible to determine the metes and bounds of the claimed invention.

e. Claim 8 is indefinite for reciting "the immunomodulating agent comprises an antibody-antigen complex" because it is not clear which portion is the antigen and which portion is the antibody. Is the claim meant to recite an antibody (Fc receptor ligand?) bound to the T cell peptide antagonist?

f. Claim 11 is indefinite for reciting "wherein said T cell receptor antagonist is expressed within at least one complementarity determining region" as it is not clear whether the antagonist replaces the CDR or whether the antagonist is placed within the CDR, such that the CD, together with the other CDRS, is still able to bind antigen.

6. Claims 9-11 and 29 are rejected under 35 U.S.C. § 112, first and second paragraph, as the claimed invention is not described in such full, precise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and

distinctly claim the subject matter which applicant regards as the invention. The claims are indefinite for reciting "chimeric" as the exact meaning of the word is not known. The term chimeric is generic to a class of antibodies which are products of genetic shuffling of antibody domains and other active proteins. The term encompasses antibodies fused to non-immunoglobulin proteins as well as antibodies wherein any domain of the antibody is substituted by corresponding regions or residues of human antibodies including but not limited to CDR grafted antibodies. In absence of a single defined art recognized meaning for the phrase and lacking a definition of the term in the specification, one of skill in the art could not determine the metes and bounds of the claims.

a. The specification does not enable chimeric antibodies commensurate in scope with the claims, as only chimeric antibodies having murine variable regions and human constant regions have been contemplated. The technology required to produce CDR grafted chimeric antibodies was in its early stages of development and was highly unpredictable at the time applicant's invention was made. Modifications of the variable region which are involved in the production of CDR grafted chimeric antibodies often affect the specificity and affinity due to changes in the three dimensional conformation of the variable region. Loss of affinity is generally expected to adversely affect the therapeutic effectiveness of a monoclonal antibody. The specification provides no guidance or direction to one of ordinary skill in the art regarding how to produce CDR-grafted chimeric antibodies not other types of chimeric antibodies. Furthermore, there is no guidance in the specification for the production of other types of fusion proteins which would fall

in the category of "chimeric" antibody. Undue experimentation would be required of one skilled in the art to produce mouse/human chimeric antibodies commensurate in scope with the claimed invention using the instant specification for guidance. Further to the above discussion, the specification provides no teaching or direction with respect to the myriad chimeric molecules in any particular application.

7. Claims 1-4, 6-11, 22-24 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

a. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically

affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an IL-1ß antibody in unspecified order and fused to any human or nonhuman framework sequence, have the required binding function. The specification provides no direction or guidance regarding how to produce fusion proteins and antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional humanize antibody can be obtained by replacing the CDR regions of an acceptor antibody with the CDRs of a donor antibody. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Additionally, Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

8. The claims 22-24 and 26-29 are drawn to a pharmaceutical composition for endocytic presentation of an immunosuppressive factor on the surface of an antigen presenting cell of a vertebrate comprising at least one immunomodulating agent. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent

with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions is for the "treatment of autoimmune disease, facilitation of tissue or organ transplant and the mitigation of symptoms produced by allergens" (p. 11, paragraph 3). Thus, the nature of the invention is an immunogenic/therapeutic composition used in the treatment of immunosuppression by endocytic presentation of an immunosuppressive factor.

a. Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, *viz.*, for the suppression of the immune response in autoimmune diseases.

b. At the time the invention was made, pharmaceutical compositions comprising the claimed immunosuppressive factors were not routinely used for the treatment of autoimmune diseases. The specification lacks guidance by way of general methods or working examples which teach an "effective amount" of the polypeptide which would be used for this purpose.

c. Concerning claims 1-4, 5-11, 22-24, 26-29, there is a great deal of art-recognized unpredictability in the area of immunosuppression via the endocytic presentation of T cell antagonists. See for example, Sercarx et al (Annu rev Immunol. 1993 Vol 11:729-66 PTO 1449, Paper 5, reference T), in which "the molecular context of the determinant was paramount in determining the result of antigen processing. Sites sensitive to proteolytic enzymes may differ even among closely related antigens" (page 739, bottom). The same peptide, MBP, may be presented differently "for exogenous antigen in the lymph node than for endogenous protein in the

CNS" (page 751, last paragraph). Sercarx sums up the dominance and crytpicity of T cell antigenic determinants "as well as daunting complexity" (last paragraph).

d. Sebzda et al (Science Vol 263 3/94, 1615-1616, PTO 1449, paper 5, reference S) provide evidence that even the same peptide can both positively and negatively select T cells, and that whether the event is immunosuppressive or immunoenhancing is dependent only upon the "numbers of TCRs engaged with MHC molecule at a given time" (page 1618, final paragraph). The broadly written claims are not limited to a certain dose of immunosuppressive agent and encompass amounts that, as shown by Sebzda et al, would be capable of both mediating positive and negative selection on T cells.

e. This unpredictability is further supported by Jameson et al (Annu rev Imunol Vol 13 93-126, 1995, PTO 1449, Paper no 5, reference K). Jameson et al teach that 'some high affinity ligands can drive positive selection in a very narrow concentration range... above this concentration, they mediate negative selection" (page 116, second paragraph, page 117 first full paragraph, Figure 3). Jameson et al summarize that "Different T cells may be positively selected in different ways" and that the number of suitable ligands "may well be unmanageable experimentally" (page 118, third and fourth full paragraphs).

f. Applicant is also directed to Jameson et al (J Exp Medicine Vol 177 j/93, 1541-1550, PTO 1449, paper no 5, reference J, pages 1548, paragraphs (b) and (d)); Hsu et al (J Exp Medicine Vol 181 2/95 805-810, PTO 1449, paper 5, reference I, final paragraph of page 809)); Feldman et al (Cell Vol 85, 301-310 5/96, PTO 1449, Paper no 5, reference H, page 307, second

column, first full paragraph and page 309, final paragraph), Evavold et al (Science Vol 252, 5/91, 1308 PTO 1449 Paper no 5, reference G, Table 1) and the abstract of Evavold et al (Immunology Today, Vol 14 No 12 602, 1993, PTO 1449 paper 5, reference F) for various other examples of the unpredictability of modulating or suppressing the immune response with endocytically presented T cell peptides antagonists.

g. Although it can be argued that humoral/cellular immune responses are necessary for immunosuppression, it is unpredictable whether such responses are sufficient to enable a composition, particularly in view of the minimal guidance in the specification regarding a predictive link or nexus between such responses and the treatment or prevention of any disease. The specification does not provide guidance sufficient to enable the skilled artisan to link, in a predictable way, the use of the broadly claimed immunosuppressive agents as a pharmaceutical composition and the suppression of a protective immune response therewith. In view of this limited guidance, the skilled artisan is presented with a multitude of diseases against which the "pharmaceutical composition" must be evaluated, with few facts upon which a prediction of efficacy may be made.

h. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of autoimmune disease using the multitude of factors and agents and analogs broadly encompassed by the claims. It is unpredictable whether the claimed pharmaceutical compositions, which are disclosed as being immunosuppressive, would have the added property of suppressing an immune response sufficient

to inhibit autoimmune responses, because the specification has not disclosed a link or nexus between the broadly claimed factors and analogs and their effectiveness in treating autoimmune diseases in humans. Further, it is not routine in the art of immuno therapy to use compositions analogous to the claimed compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed composition effective for its intended use. Therefore, undue experimentation would be required to make and use the invention.

i. The claims recite the endocytic presentation of immunosuppressive agents. The specification teaches that these agents would be T cell receptor peptide antagonists. The specification discloses that the T cell antagonist is a peptide that binds MHC Class II structures and T cell receptors, however, does not promote activation of the T cell (see page 12, lines 2-7). One skilled in the art would reasonably conclude that the presentation and binding of the T cell antagonist shares common prerequisites as the presentation and binding of the T cell antagonists in that they both must (1) be endocytically presented, (2) by MHC Class II and (3) bind to both MHC Class II and T cell receptor on the cell surface. As evidenced by Livingstone et al (1987 An Rev Immunology Vol 5 477-501), T cell epitopes are generally at least 7 amino acids long and that increasing peptide length often results in increased antigenic potency and that antigenicity of T cell epitopes "may crucially depend upon the ability of peptides to adopt appropriate secondary structures (see page 496, last paragraph). Furthermore, Livingstone et al disclose that "further analysis however suggested that the definition of an [T cell] epitope could

be rather more complicated" (pages 483-484, bridging paragraph) than merely the primary amino acid length of 7 amino acids. Moreover, Livingstone state that "experiments highlight one problem that continually arises... the designation of any peptide as stimulatory or non-stimulatory is an arbitrary one". Livingstone et al state that "the definition of an [T cell] epitope thus depends both on the antigen sensitivity of the T-cell clone in question and on arbitrarily imposed limits on the maximum concentration of peptide" (see page 484, first paragraph). Livingstone et al caution that which regards to the question of peptide length on antigenic potency, the "resolution of this question will probably have to wait until the structure of this ternary complex is elucidated". Thus, the Livingstone et al reference clearly demonstrates that the identification of a T cell epitope is dependent upon more than just a particular length of peptide and that amino acid residues outside the seven are important for antigenicity. Additionally, Livingstone et al teach that although two models are available to determine T cell epitopes, both models depend upon the unpredictable and arbitrary designation of peptide stimulation. Livingstone et al also teach that it is the ternary structure of the peptide is necessary for determining the identification of T cell epitopes. One skilled in the art would reasonably conclude that in view of the lack of guidance in the specification concerning T cell peptide antagonist identification the identification of T cell epitopes and antagonists thereof would require undue experimentation.

j. The specification does not disclose how to use the instant invention for the treatment of disease in humans. Claims 22-24 and 26-29 read on pharmaceutical compositions for treating individuals, which encompasses humans. Applicant has not enabled the breadth of the

claimed invention in view of the teachings of the specification because the use of the instant invention disclosed in the specification is the in vivo treatment of humans. The state of the art is such that is unpredictable in the absence of in vivo data (as per the specification) as to whether the instant invention can be used for the treatment of human disease. Hurtenbach et al (J Exp Medicine Vol 177 1499-1504 1993) teaches that peptide administration can provoke "severe immunological side effects" (see page 1503, second column). Hurtenbach et al teach that peptides are currently unsuitable for therapeutic use (see page 2503, second column, last two lines).

k. Regarding the use of peptides for therapeutic purposes, pharmaceutical therapies in the absence of appropriate in vivo data establishing that said peptides can be used for the treatment of humans are unpredictable for the following reasons; (1) the peptide may be inactivated before producing an effect, i.e., proteolytic degradation, immunological inactivation or due to the inherently short half life of the peptide; (2) the peptide may not reach the target area because i.e. the protein may not be able to cross the mucosa or the protein may be absorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the peptide unsuitable for in vivo therapeutic use, i.e., such as an adverse side effects prohibitive to the use of such a treatment, See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat. App. And inter. 1992).

l. The specification has not provided evidence that mice can be tolerized to any T cell epitope, or even any PLP protein as alleged in Example X of the specification. The

specification only teaches the PLP1 peptide for in vitro studies and for in vivo studies using a mouse model. The specification fails to provide correlation between the results obtained in vivo animal model and those expected in humans. As evidenced by Kuchroo et al, J Immunology Vol 153:3326 1994, PTO 1449 Paper no 5, reference N), the results obtained by administering TCR antagonist peptides from proteolipid protein in the SJL mice model (comparable with Example VII, IX, X, XII of the specification) present "a striking...disparity between clinical signs and histologic lesions" which was 'reported by other groups" (page 3335, first column, last paragraph). Kuchroo et al summarize that the "presence of inflammatory foci may not correlate with the clinical disease". One skilled in the art would reasonably conclude that if the histologic results obtained in the mouse model do not correlate with the mouse clinical disease, then it would be unpredictable to extrapolate that any results obtained with the mouse model would correlate with results expected from the treatment of humans.

m. There is not guidance in the specification as to how to determine which antagonists peptide or combination of antagonist peptides can be administered to any particular individual for the treatment of autoimmune. It appears that undue experimentation would be required of one skilled in the art to practice the instant claimed invention using the teachings of the specification. See Ex parte Forman, 230 USPQ 546 BPAI, 1986.

n. The specification is not enabling for an isolated portion of a peptide that contains a T cell epitope wherein said isolated portion is derived from the peptides disclosed in the specification. The specification is also not enabled for a T cell antagonist smaller than the specific

peptides disclosed in the specification. There is not disclosure in the specification of the specific minimal T cell antagonist recognized in any of the peptides disclosed in the specification. There is not guidance in the specification as to how to the identity of said T cell antagonists would be ascertained. Since the specification has not identified which amino acids are critical or essential characteristics of the T cell antagonists, or of the peptides of various lengths encompassed by the terminology of the claims, there is a lack of sufficient guidance to determine which amino acids substitutions or protein domain alterations could be made without altering the fundamental characteristics of the immunosuppressive factors and there are no working examples of any such variants.

o. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as evidenced by Ashton-Rickardt et al (Cell Vol 76 651-663 2/94, PTO 1449 Paper no 5, reference A), T cell positive and negative selection dependent upon the "structure of MHC-bound peptide was found to be a highly selective to even small sequence differences" (page 659, second column, first paragraph). Ashton -Rickardt et al teach that "the substitution of just one amino acid has the potential either to abolish or to reduce the ability of a peptide to select" (page 658, second column, second full paragraph). Applicant is also directed to the teachings of Rudikoff et al, cited above concerning the unpredictability of determining the effects on antigen affinity by single amino acid changes in an antibody's CDR.

p. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the

biological activity of the protein. Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. Elucidation off the genetic code induces one to believe that one can readily obtain a functional synthetic protein for any known nucleic acid sequence with predictable results.

q. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention. Since the state of the art of protein modification suggests that the effects of sequence alterations are unpredictable and since the art widely teaches the complexity and uncertainty of generating suppressive responses using T cell peptide antagonists, and since the specification provides no guidance as to which peptides would result in an active protein capable of modifying the autoimmune response, undue experimentation would be required to determine which peptides would be able to function as the PLP protein or other immunosuppressive agent with all its identifying characteristics. In absence of such guidance and/or working examples, one skilled in the art would reasonably conclude that a large number of peptides could be made, however, the specification has not taught how all the molecules would be T cell peptide antagonists that can modify the immune response upon administration.

Claim Rejections - 35 U.S.C. § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4, 6-11, 22-24, 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuchroo et al (J Immunology Vol 148 3776-3782 6/92, PTO 1449, Paper no 5, reference M); Mueller et al (WO 96/34622, published Nov 96, PTO 1449, paper no 7); in combination with WO 94/14847 (7/94 Zanetti et al, PTO 1449, Paper no 5), Zanetti et al, US Patent 5,508,386; Kappler et al (WO 95/23814 9/95, PTO 1449, Paper no 7); Selick et al (WO 93/10220 3/93, PTO 1449 paper no 7) and Bona et al (Cellular and Molecular Biology Vol 40 (Suppl I) 21-30 1994).

a. The claims recite an immunomodulating agent for endocytic presentation of an immunosuppressive factor on the surface of an antigen presenting cell of a vertebrate comprising at least one Fc receptor ligand and at least one immunosuppressive factor. The claims also recite a immunosuppressive factor that is a T cell receptor peptide antagonist capable of activating a T cell response to proteolipid protein; wherein the Fc receptor ligand comprises at least part of a domain of a constant region of an immunoglobulin molecule, wherein the immunomodulating agent comprises a polypeptide, an antigen-antibody complex, a chimeric antibody and wherein the T cell receptor antagonist is expressed within at least one complementarity determining region. Other embodiments include pharmaceutical compositions and antagonist analogs.

b. Kuchroo et al teach synthetic peptides 139-151 which engages a heterogenous T cell repertoire and suggest that this peptide must be considered a possible immunotherapy in the autoimmune disease multiple sclerosis (see Abstract and final paragraph). Mueller et al teach a variety of human proteolipid proteins for the treatment of autoimmune diseases such as multiple sclerosis

c. Zanetti et al (1994 or 1996) teach the introduction of oligopeptide epitopes for expression within the three dimensional fold of an immunoglobulin molecule, thus creating molecules useful to induce specific biologically active anti-receptor immunity. These immunoglobulin molecules contain part of the constant region. Zanetti et al (!994) teach that administering such molecules would be useful for building tolerance (that is, T cell suppression) to certain antigens, including those associated with autoimune disease, or for down regulating hypersensitivity to allergens" (page 6, last paragraph). Zanetti et al teach chimeric (humanized antiodies (see Column 5, lines 22-27, of '386).

d. Either of Kappler et al or Selick et al teach methods to make polypeptide T cell receptor antagonists for the treatment of autoimune diseases by linking antigenic peptides to portions of an and endocytically processed cell surface receptor MHC.

e. Bona et al teach the immunogenicity of peptides that are grafted onto immunoglobulin molecules that contain constant regions. Bona et al teach that the grafted immunoglobulins are "taken up by various types of APCs (antigen presenting cells) and that "their internalization is mediated via Fc receptors" (page 23, second column (e)). Bona et al also teach that the administration of biologically important antigen can be used in the therapy of autoimune disease. Bona et al predict that immunoglobulin-antigen peptides will be "more efficient for peptide competition" (page 29, last paragraph).

f. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to produce the claimed invention because

i. Bona et al, Kappler et al and Selick et al teach endocytic presentation of surface receptors containing antigens to act as T cell receptor antagonists for the treatment of autoimmune disease

ii. Bona et al, and either Zanetti reference teach the addition of peptides to a molecule comprising the Fc receptor comprising at least part of a constant region domain.

iii. Mueller et al and Kuchroo et al teach immunosuppressive T cell peptides from proteolipid protein and their use in the treatment of autoimmune disease.

Moreover, one skilled in the art would have had a reasonable expectation of success of making the immunosuppressive agent because Bona et al clearly teaches that an immunoglobulin containing a peptide antigen is taken up by antigen presenting cells, internalized via their Fc receptors and endocytically processed as shown in figure 4 and Zanetti et al teach that these molecules would be useful for immunosuppression via building tolerance to autoimmune antigens and because either of Kuchroo et al or Mueller et al teach specific proteolipid peptides involved in immunosuppression. One skilled in the art would have been motivated to make the claimed compounds in view of the success (1) Mueller et al and Kuchroo et al had in suppressing the immune system with PLP peptides and (2) Zanetti had in delivering an epitope to the surface of antigen presenting cells by using a immunoglobulin molecule comprising the Fc receptor grafted to the peptide (3) Selick et al and Kappler et al had in linking peptides to endocytically processed MHC moelculaes for T cell antagonists and in view of the (4) prediction of Bona et al that autoimmune antigens could be successfully grafted onto Fc bearing molecules for MHC

presentation to T cells. Furthermore, one skilled in the art would have been motivated to combine the references to make the claimed immunosuppressive agent because bona et al teach the Ig bearing epitopes will be more efficient in peptide competition therapy. The resulting immunosuppressive molecules would comprise an Fc receptor ligand, would comprise a polypeptide and be considered chimeric. If the claims intend "chimeric" to mean "humanized", Zanetti et al teach this limitation.

Because pharmaceutically acceptable carriers such as sterile saline solution and phosphate-buffered-saline solution were well known in the art, one of ordinary skill would have known how to formulate a pharmaceutical composition comprising a carrier/excipient and the instantly claimed polypeptide or fragments thereof. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore the invention, as a whole, was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

13. The following reference is made of record and cited as being of interest to the instant application:

a. Legge et al (J Exp Med Vol 185 No 6 3/97 1043-1053).

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Reeves, Ph.D., whose telephone number is (703) 308-7553. The examiner can normally be reached on Monday through Friday from 8:00 am to 5:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

17. All Internet e-mail communications will be made of record in the application file. **PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122.** This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

18. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

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